09/25/2005 10669301.trn

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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JUL 20   Powerful new interactive analysis and visualization software,
                   STN AnaVist, now available
 NEWS  4  AUG 11   STN AnaVist workshops to be held in North America
 NEWS  5  AUG 30   CA/CAplus -Increased access to 19th century research documents
 NEWS  6  AUG 30   CASREACT - Enhanced with displayable reaction conditions
 NEWS  7  SEP 09   ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  8  SEP 22   MATHDI to be removed from STN

 NEWS EXPRESS  JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
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Enter NEWS followed by the item number or name to see news on that specific topic.

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*FEDRIP - Federal Research in Progress Database

* The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 15:04:26 ON 25 SEP 2005

=>
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THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
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Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 15:04:38 ON 25 SEP 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6
DICTIONARY FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

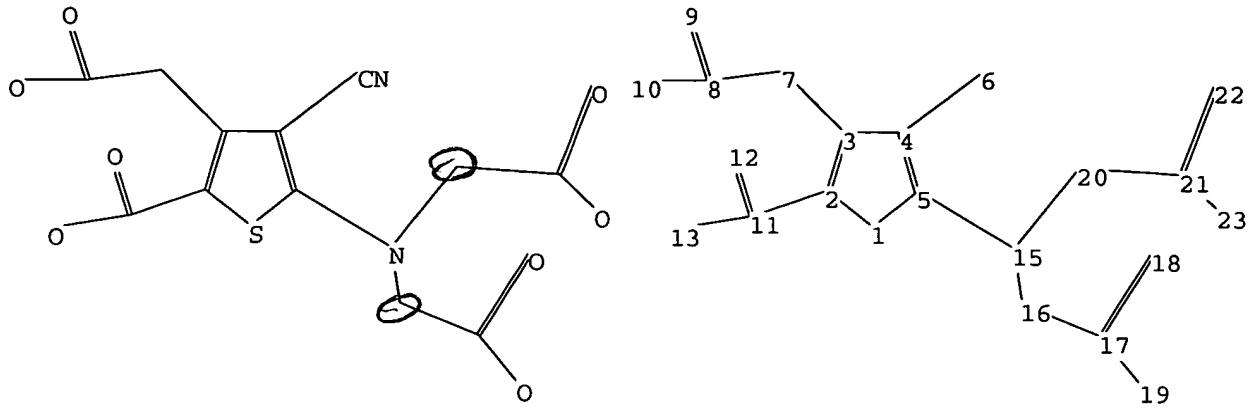
Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10669301.str

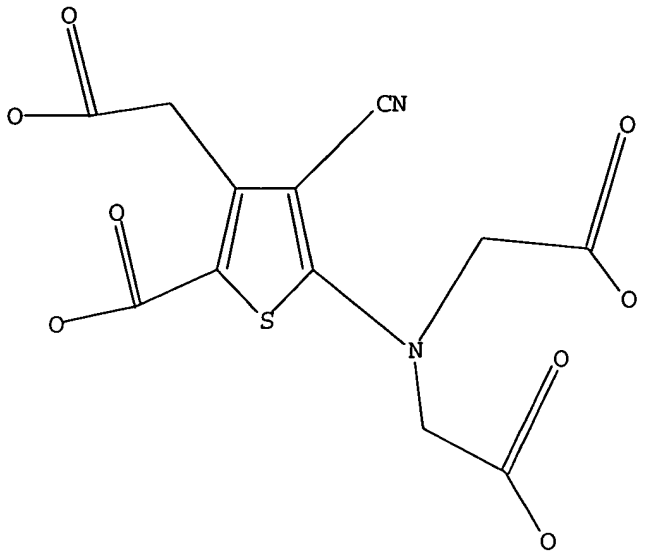


chain nodes :
6 7 8 9 10 11 12 13 15 16 17 18 19 20 21 22 23
ring nodes :
1 2 3 4 5
chain bonds :
2-11 3-7 4-6 5-15 7-8 8-9 8-10 11-12 11-13 15-16 15-20 16-17 17-18
17-19 20-21 21-22 21-23
ring bonds :
1-2 1-5 2-3 3-4 4-5
exact/norm bonds :
5-15 8-9 8-10 11-12 11-13 15-16 15-20 17-18 17-19 21-22 21-23
exact bonds :
1-2 1-5 2-3 2-11 3-4 3-7 4-5 4-6 7-8 16-17 20-21
isolated ring systems :
containing 1 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> s l1
SAMPLE SEARCH INITIATED 15:04:54 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        2 TO ITERATE

100.0% PROCESSED         2 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            2 TO      124
PROJECTED ANSWERS:               0 TO        0

L2             0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 15:05:00 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       55 TO ITERATE

100.0% PROCESSED        55 ITERATIONS                              11 ANSWERS
SEARCH TIME: 00.00.01

L3            11 SEA SSS FUL L1

=> FIL HCAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   161.33     161.54

FILE 'HCAPLUS' ENTERED AT 15:05:06 ON 25 SEP 2005
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 25 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 23 Sep 2005 (20050923/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

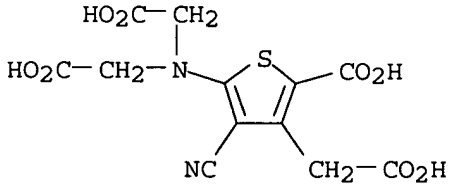
```
=> s l3
L4           55 L3

=> s l4 and process
        2149075 PROCESS
        1438162 PROCESSES
        3197607 PROCESS
                (PROCESS OR PROCESSES)
L5            9 L4 AND PROCESS

=> s l5 and morpholine
          32190 MORPHOLINE
           1162 MORPHOLINES
          32642 MORPHOLINE
                (MORPHOLINE OR MORPHOLINES)
L6            2 L5 AND MORPHOLINE

=> d l5 ibib abs hitstr tot

L5   ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:240650  HCAPLUS
DOCUMENT NUMBER:          142:422811
TITLE:                    Strontium ranelate: A novel mode of action leading to
                          renewed bone quality
AUTHOR(S):                Ammann, Patrick
CORPORATE SOURCE:         Division of Bone Diseases, WHO Collaborating Center
                          for Osteoporosis Prevention, Department of
                          Rehabilitation and Geriatrics, University Hospital of
                          Geneva, Geneva, 1211/14, Switz.
SOURCE:                   Osteoporosis International (2005), 16(Suppl. 1),
                          S11-S15
                          CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER:                Springer London Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review. Various bone resorption inhibitors and bone stimulators have
     been shown to decrease the risk of osteoporotic fractures. However, there
     is still a need for agents promoting bone formation by inducing pos.
     uncoupling between bone formation and bone resorption. In vitro studies
     have suggested that strontium ranelate enhances osteoblast cell
```

replication and activity. Simultaneously, strontium ranelate dose-dependently inhibits osteoclast activity. In vivo studies indicate that strontium ranelate stimulates bone formation and inhibits bone resorption and prevents bone loss and/or promotes bone gain. This pos. uncoupling between bone formation and bone resorption results in bone gain and improvement in bone geometry and microarchitecture, without affecting the intrinsic bone tissue quality. Thus, all the determinants of bone strength are pos. influenced. In conclusion, strontium ranelate, a new treatment of postmenopausal osteoporosis, acts through an innovative mode of action, both stimulating bone formation and inhibiting bone resorption, resulting in the rebalancing of bone turnover in favor of bone formation. Strontium ranelate increases bone mass while preserving the bone mineralization **process**, resulting in improvement in bone strength and bone quality.

IT **135459-87-9**, Strontium ranelate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium ranelate stimulate bone formation, inhibits resorption balances bone turnover thus increases bone mass, preserves bone mineralization **process** in turn improves bone strength, quality in postmenopausal osteoporotic woman)

RN 135459-87-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:270007 HCAPLUS

DOCUMENT NUMBER: 140:287532

TITLE: Preparation of substituted phosphonate compounds having bone anabolic activity

INVENTOR(S): Nguyem, Lan Mong; Diep, Vinh Van; Phan, Hieu Trung; Niesor, Eric Joseph; Masson, Daniele; Guyon-Gellin, Yves; Buattini, Emanuele; Severi, Carlo; Azoulay, Raymond; Bentzen, Craig Leigh; et al.

PATENT ASSIGNEE(S): Ilex Oncology Research, S.a r.l., Switz.

SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026245	A2	20040401	WO 2003-US29392	20030918
WO 2004026245	A3	20040610		
WO 2004026245	C1	20040722		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-412091P P 20020919

OTHER SOURCE(S): MARPAT 140:287532

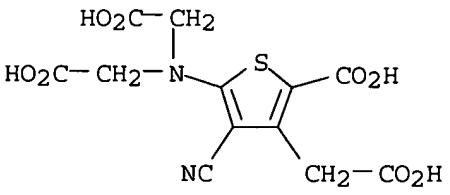
AB The present invention relates to the use of substituted phosphonate compds. with bone anabolic activity in the treatment and-or prevention of bone diseases, such as osteoporosis. Thus, TiCl4/N-methylmorpholine mediated reaction of 3,5-di-tert-butyl-4-hydroxybenzaldehyde with di-Me 2-oxopropylphosphonate gave 38% title compound, 3,5-(t-Bu)2-4-HOC6H2CH:CHCOCH2PO3Me2; reduction of HMG-CoA reductase with prepared compds. is given.

IT **135459-87-9**, S-12911

RL: BCP (Biochemical process); BIOL (Biological study); PROC (Process) (preparation of substituted keto phosphonate compds. starting from aromatic aldehydes and their bone anabolic activity)

RN 135459-87-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

L5 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:267250 HCAPLUS

DOCUMENT NUMBER: 140:303853

TITLE: Preparation of substituted ketophosphonate compounds having bone anabolic activity

INVENTOR(S): Nguyen, Lan Mong; Diep, Vinh Van; Phan, Hieu Trung; Niesor, Eric Joseph; Masson, Daniele; Guyon-Gellin, Yves; Buattini, Emanuele; Severi, Carlo; Azoulay, Raymond; Bentzen, Craig Leigh

PATENT ASSIGNEE(S): Ilex Oncology Research, S.a r.l., Switz.

SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004026315	A1	20040401	WO 2003-US29080	20030918
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1551418	A1	20050713	EP 2003-752401	20030918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

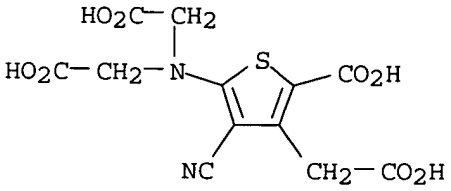
PRIORITY APPLN. INFO.: US 2002-412091P P 20020919
WO 2003-US29080 W 20030918

OTHER SOURCE(S): MARPAT 140:303853

AB The present invention provides preparation of substituted ketophosphonate compns. of matter, pharmaceutical compns. and methods of use of such compns. for the treatment and/or prevention of bone diseases. Thus, TiCl4/N-methylmorpholine mediated reaction of 4-hydroxy-3-methoxy-5-methylbenzaldehyde with di-Me 1,1-dimethyl-2-oxopropylphosphonate in THF gave 41% title compound, di-Me 4-(3-methoxy-5-methyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-ylphosphonate, 3-MeO-5-Me-4-HOC6H2CH:CHCOCMe2PO3Me2; reduction of amount of HMG-CoA reductase with the prepared compds. are given.

IT **135459-87-9**, S-12911
RL: BCP (Biochemical process); BIOL (Biological study); PROC (Process)
(preparation of substituted ketophosphonate compds. from aromatic aldehydes and
their bone anabolic activity)

RN 135459-87-9 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:253137 HCAPLUS
DOCUMENT NUMBER: 140:287258
TITLE: **Process** for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
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WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
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JP 2004269495	A2	20040930	JP 2003-330438	20030922
AT 286041	E	20050115	AT 2003-292317	20030922
ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
SG 110070	A1	20050428	SG 2003-5554	20030924

PRIORITY APPLN. INFO.: FR 2002-11764 A 20020924
OTHER SOURCE(S): CASREACT 140:287258
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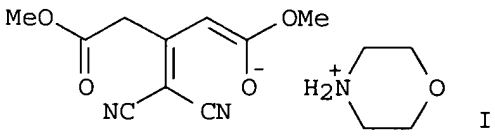


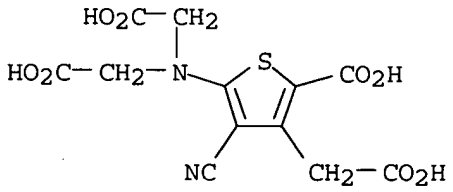
I

AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of morpholine per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

IT **135459-87-9P**, Strontium ranelate **135459-89-1P**
RL: IMF (Industrial manufacture); PREP (Preparation)
(**process** for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 135459-87-9 HCAPLUS

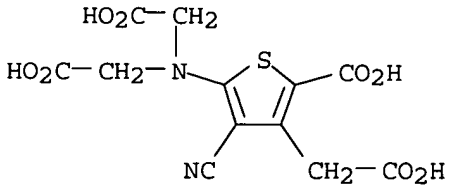
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

RN 135459-89-1 HCAPLUS

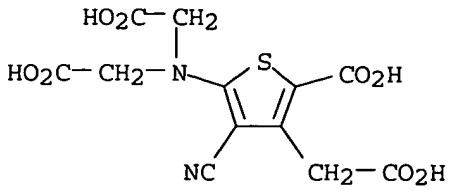
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, magnesium salt (1:2) (9CI) (CA INDEX NAME)



●2 Mg

IT **135459-90-4P**, Ranelic acid
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**process** for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

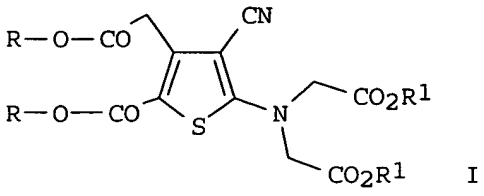
RN 135459-90-4 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:252227 HCAPLUS
DOCUMENT NUMBER: 140:270729
TITLE: . **Process** for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059134	A1	20040325	US 2003-669302	20030924
FR 2844797	A1	20040326	FR 2002-11765	20020924
FR 2844797	B1	20041022		
EP 1403265	A1	20040331	EP 2003-292318	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029034	A1	20040408	WO 2003-FR2775	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004269496	A2	20040930	JP 2003-330439	20030922
CA 2442881	AA	20040324	CA 2003-2442881	20030923
NZ 528401	A	20040528	NZ 2003-528401	20030923
ZA 2003007411	A	20040707	ZA 2003-7411	20030923
BR 2003004203	A	20040824	BR 2003-4203	20030923
CN 1500784	A	20040602	CN 2003-134812	20030924
SG 110069	A1	20050428	SG 2003-5553	20030924

PRIORITY APPLN. INFO.: FR 2002-11765 A 20020924
OTHER SOURCE(S): CASREACT 140:270729; MARPAT 140:270729
GI



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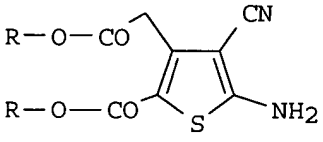


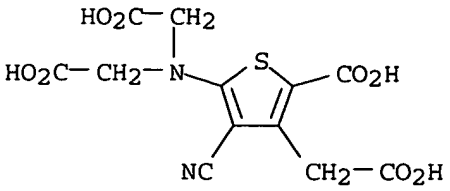
II

AB Tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid [I; R, R1 = (un)branched C1-6 alkyl] are prepared in high yield and selectivity by the alkylation of the corresponding 5-amino compound (II) with an alkyl bromoacetate ester BrCH2CO2R1 in the presence of a catalytic amount of a quaternary ammonium compound, potassium carbonate acid scavenger at reflux in an organic solvent, the reaction mixture is then concentrated by distillation, an a nonsolvent added to cause precipitation of the product with cooling. The synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

IT **135459-87-9P 135459-88-0P 135459-89-1P**
135459-90-4P, Ranelic acid **674773-13-8P**
674800-87-4P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(**process** for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates)

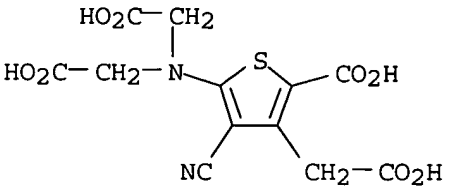
RN 135459-87-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



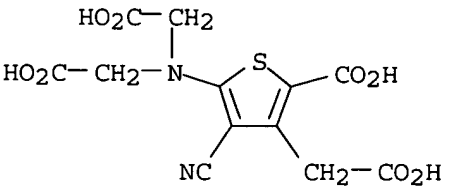
●2 Sr

RN 135459-88-0 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, calcium salt (1:2) (9CI) (CA INDEX NAME)



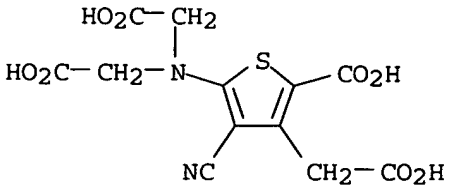
●2 Ca

RN 135459-89-1 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, magnesium salt (1:2) (9CI) (CA INDEX NAME)

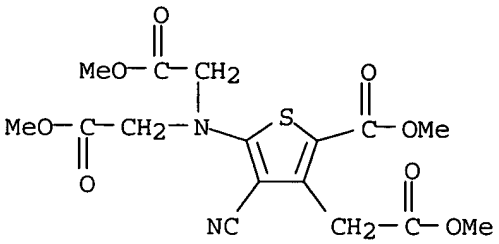


●2 Mg

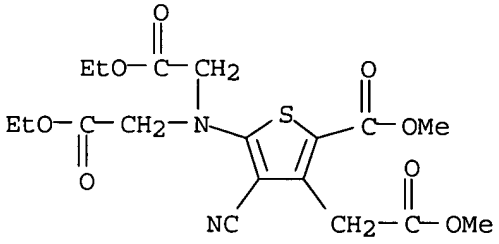
RN 135459-90-4 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



RN 674773-13-8 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



RN 674800-87-4 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



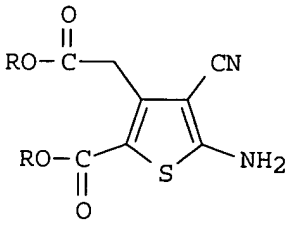
L5 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:249307 HCAPLUS
DOCUMENT NUMBER: 140:272696
TITLE: New process for industrial synthesis of strontium ranelate and its hydrates
INVENTOR(S): Vaysse, Ludot Lucile; Lecouve, Jean Pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
SOURCE: Fr. Demande, 22 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029036	A1	20040408	WO 2003-FR2777	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004149516	A2	20040527	JP 2003-330440	20030922
CA 2442878	AA	20040324	CA 2003-2442878	20030923
ZA 2003007409	A	20040707	ZA 2003-7409	20030923
NZ 528402	A	20040730	NZ 2003-528402	20030923
BR 2003004213	A	20040831	BR 2003-4213	20030923
US 2004063972	A1	20040401	US 2003-669301	20030924
CN 1496986	A	20040519	CN 2003-134813	20030924
SG 110071	A1	20050428	SG 2003-5555	20030924
PRIORITY APPLN. INFO.:			FR 2002-11763 A	20020924

OTHER SOURCE(S): MARPAT 140:272696

GI



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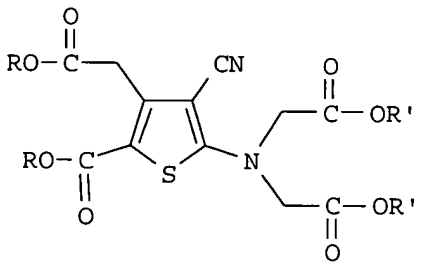


II

AB An industrial **process** for the synthesis of strontium ranelate and its hydrates consists of: reaction of RO2CCH2COCH2CO2R (R = linear or branched C1-6 alkyl) with malononitrile (NCCH2CN) in MeOH in presence of morpholine (>0.95 mol per mol diester) to give the morpholinium salt of ROCOCH2C[:C(CN)2]CH:C(OR)O-, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with BrCH2CO2R' (R' = e.g., Me or Et) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K2CO3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with Sr(OH)2 at reflux in water for ≥ 5 h to give strontium ranelate and its hydrates. Thus, the octahydrate of strontium ranelate was prepared by this method (96% yield and 98% purity in final step).

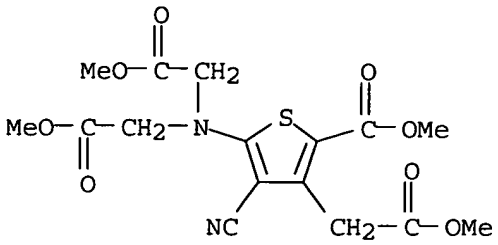
IT **674773-13-8P**

RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

(for industrial preparation of strontium ranelate and its hydrates)

RN 674773-13-8 HCAPLUS

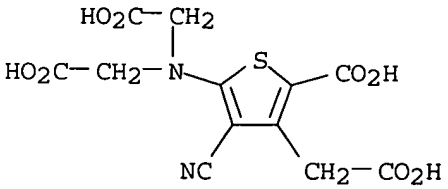
CN 3-Thiopheneacetic acid, 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)

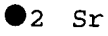


IT **135459-87-9P**, Strontium ranelate **674773-07-0P**
674773-15-0P
RL: IMF (Industrial manufacture); PREP (Preparation)
(industrial preparation of)

RN 135459-87-9 HCAPLUS

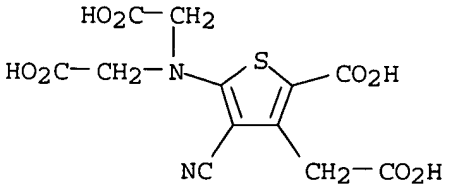
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)

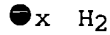


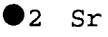


RN 674773-07-0 HCAPLUS

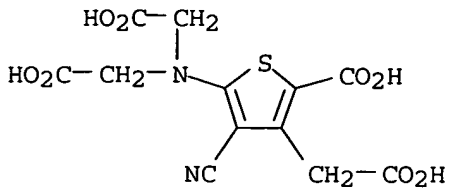
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2), hydrate (9CI) (CA INDEX NAME)







RN 674773-15-0 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2), octahydrate (9CI) (CA INDEX NAME)



●8 H_2O

●2 Sr

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

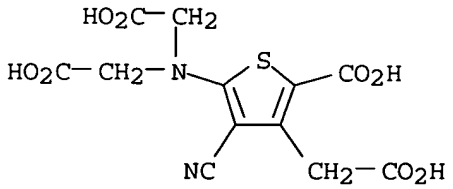
L5 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:253517 HCAPLUS
DOCUMENT NUMBER: 139:127362
TITLE: A nonlinear compartmental model of Sr metabolism. I. Non-steady-state kinetics and model building
AUTHOR(S): Staub, J. F.; Foos, E.; Courtin, B.; Jochemsen, R.; Perault-Staub, A. M.
CORPORATE SOURCE: Unite Mixte de Recherches 7052 Centre National de la Recherche Scientifique, Laboratoire de Recherches Orthopediques, Faculte de Medecine Lariboisiere-St-Louis, Paris, 75010, Fr.
SOURCE: American Journal of Physiology (2003), 284(3, Pt. 2), R819-R834
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A model of Sr metabolism was developed by using plasma and urinary Sr kinetic data obtained in groups of postmenopausal women who received 4 different oral doses of Sr and collected during the Sr administration period (25 days) and for 28 days after cessation of treatment. A nonlinear compartmental formalism that is appropriate for study of non-steady-state kinetics and allows dissociation of variables pertaining to Sr metabolism (system 1) from those indirectly operating on it (system 2) was used. At each stage of model development, the dose-dependent model response was fitted to the 4 sets of data considered simultaneously (1 set per dose). A 7-compartment model with internal Sr distribution and intestinal, urinary, and bone metabolic pathways was selected. It includes 2 kinds of nonlinearities: those accounting for saturable intestinal and bone **processes**, which behave as intrinsic nonlinearities because they are directly dependent on Sr, and extrinsic nonlinearities (dependent on

system 2), which suggest the cooperative involvement of plasma Sr changes in modulating some intestinal and bone mineral metabolic pathways. With the set of identified parameter values, the initial steady-state model predictions are relevant to known physiol., and some peculiarities of model behavior for long-term Sr administration were simulated.

IT **135459-87-9**, S-12911
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonlinear compartmental model of strontium metabolism in women given oral Sr (S-12911))

RN 135459-87-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:315356 HCAPLUS
DOCUMENT NUMBER: 135:174574
TITLE: Incorporation and distribution of strontium in bone
AUTHOR(S): Dahl, S. G.; Allain, P.; Marie, P. J.; Mauras, Y.; Boivin, G.; Ammann, P.; Tsouderos, Y.; Delmas, P. D.; Christiansen, C.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Tromso, Tromso, Norway
SOURCE: Bone (New York, NY, United States) (2001), 28(4), 446-453
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

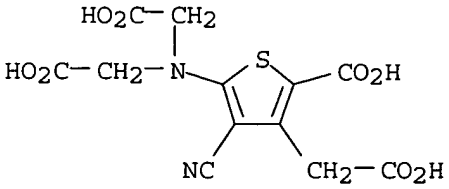
AB A review with 77 refs. The distribution and incorporation of strontium into bone has been examined in rats, monkeys, and humans after oral administration of strontium (either strontium chloride or strontium ranelate). After repeated administration for a sufficient period of time (at least 4 wk in rats), strontium incorporation into bone reaches a plateau level. This plateau appears to be lower in females than in males due to a difference in the absorption **process.** Steady-state plasma strontium levels are reached more rapidly than in bones, and within 10 days in the rat. The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated, and the strontium content of the lumbar vertebra may be estimated from iliac crest bone biopsies in monkeys. The strontium levels in bone also vary according to the bone structure, and higher amts.

of strontium are found in cancellous bone than in cortical bone. Furthermore, at the crystal level, higher concns. of strontium are observed in newly formed bone than in old bone. After withdrawal of treatment, the bone strontium content rapidly decreases in monkeys. The relatively high clearance rate of strontium from bone can be explained by the mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium. After treatment withdrawal, strontium exchanged onto the crystal is rapidly eliminated, which leads to a rapid decrease in total bone strontium levels. In summary, incorporation of strontium into bone, mainly by exchange onto the crystal surface, is dependent on the duration of treatment, dose, gender, and skeletal site. Nevertheless, bone strontium content is highly correlated with plasma strontium levels and, in bone, between the different skeletal sites.

IT **135459-87-9**, S 12911
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(incorporation and distribution of strontium in bone and plasma of rats, monkeys and humans)

RN 135459-87-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

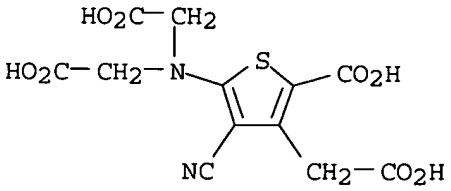
L5 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:93795 HCAPLUS
DOCUMENT NUMBER: 135:117163
TITLE: Strontium ranelate increases cartilage matrix formation
AUTHOR(S): Henrotin, Y.; Labasse, A.; Zheng, S. X.; Galais, Ph.; Tsouderos, Y.; Crielaard, J. M.; Reginster, J. Y.
CORPORATE SOURCE: Bone and Cartilage Metabolism Research Unit, University Hospital, Liege, Belg.
SOURCE: Journal of Bone and Mineral Research (2001), 16(2), 299-308
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on previous studies showing that strontium ranelate (S12911) modulates bone loss in osteoporosis, it could be hypothesized that this

drug would also be effective on cartilage degradation in osteoarthritis (OA). This was investigated in vitro on normal and OA human chondrocytes, treated or not treated with interleukin-1β (IL-1β). This model mimics, in vitro, the imbalance between chondroformation and chondroresorption **processes** observed in vivo in OA cartilage. Chondrocytes were isolated from cartilage by enzymic digestion and cultured for 24-72 h with 10-4-10-3M strontium ranelate, 10-3M calcium ranelate, or 2 + 10-3M SrCl2, with or without IL-1β or insulin-like growth factor I (IGF-I). Stromelysin activity and stromelysin content were assayed by spectrofluorometry and enzyme-amplified sensitivity immunoassay, resp. Proteoglycans (PG) were quantified by RIA. Newly synthesized glycosaminoglycans were quantified by labeled sulfate (Na235SO4) incorporation. This method allowed the PG size after exclusion chromatog. to be determined Strontium ranelate, calcium ranelate, and SrCl2 did not modify stromelysin synthesis even in the presence of IL-1β. Calcium ranelate induced stromelysin activation, whereas the strontium compds. were ineffective. Strontium ranelate and SrCl2 both strongly stimulated PG production, suggesting an ionic effect of strontium independent of the organic moiety. Moreover, 10-3M strontium ranelate increased the stimulatory effect of IGF-I (10-9M) on PG synthesis but did not reverse the inhibitory effect of IL-1β. Thus, strontium ranelate strongly stimulates human cartilage matrix formation in vitro by a direct effect effect of the strontium ion, without stimulating chondroresorption. This finding provides a preclin. basis for in vivo testing of strontium ranelate in OA.

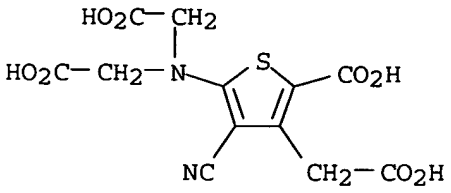
IT **135459-87-9**, S 12911 **135459-88-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(strontium ranelate, strontium chloride, and calcium ranelate effect on cartilage matrix formation)

RN 135459-87-9 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)



●2 Sr

RN 135459-88-0 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, calcium salt (1:2) (9CI) (CA INDEX NAME)



●2 Ca

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l6 ibib abs hitstr tot

L6 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:253137 HCAPLUS
DOCUMENT NUMBER: 140:287258
TITLE: **Process** for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
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WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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BR 2003004194	A	20040908	BR 2003-4194	20030922
JP 2004269495	A2	20040930	JP 2003-330438	20030922

AT 286041	E	20050115	AT 2003-292317	20030922
ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
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PRIORITY APPLN. INFO.: FR 2002-11764 A 20020924
OTHER SOURCE(S): CASREACT 140:287258
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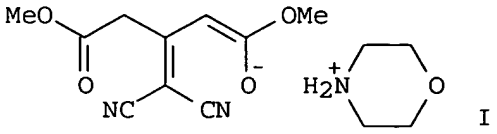
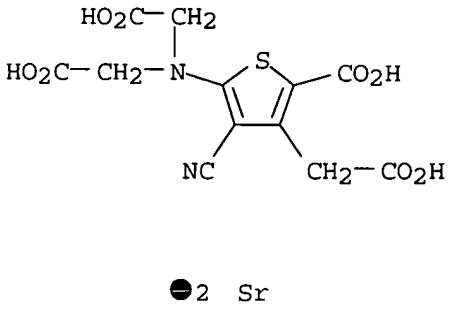


I

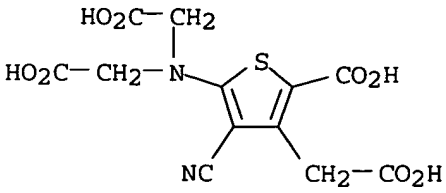
AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of **morpholine** per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

IT **135459-87-9P**, Strontium ranelate **135459-89-1P**
RL: IMF (Industrial manufacture); PREP (Preparation)
(**process** for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 135459-87-9 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)

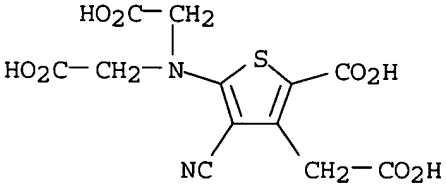


RN 135459-89-1 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, magnesium salt (1:2) (9CI) (CA INDEX NAME)



●2 Mg

IT **135459-90-4P**, Ranelic acid
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**process** for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)
RN 135459-90-4 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



L6 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:249307 HCAPLUS
DOCUMENT NUMBER: 140:272696
TITLE: New **process** for industrial synthesis of strontium ranelate and its hydrates
INVENTOR(S): Vaysse, Ludot Lucile; Lecouve, Jean Pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
SOURCE: Fr. Demande, 22 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029036	A1	20040408	WO 2003-FR2777	20030922

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2004149516	A2	20040527	JP 2003-330440		20030922
CA 2442878	AA	20040324	CA 2003-2442878		20030923
ZA 2003007409	A	20040707	ZA 2003-7409		20030923
NZ 528402	A	20040730	NZ 2003-528402		20030923
BR 2003004213	A	20040831	BR 2003-4213		20030923
US 2004063972	A1	20040401	US 2003-669301		20030924
CN 1496986	A	20040519	CN 2003-134813		20030924
SG 110071	A1	20050428	SG 2003-5555		20030924
PRIORITY APPLN. INFO.:			FR 2002-11763	A	20020924

OTHER SOURCE(S): MARPAT 140:272696
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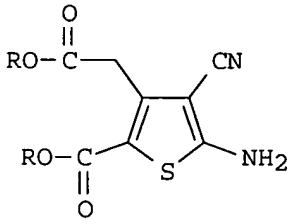

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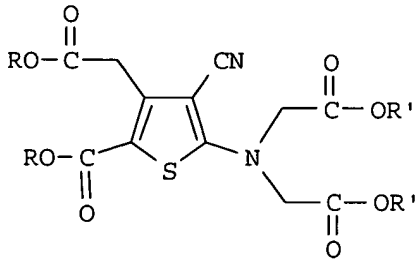


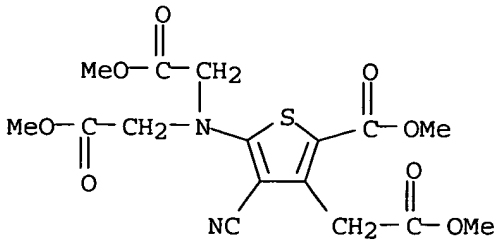
II

AB An industrial **process** for the synthesis of strontium ranelate and its hydrates consists of: reaction of RO2CCH2COCH2CO2R (R = linear or branched C1-6 alkyl) with malononitrile (NCCH2CN) in MeOH in presence of **morpholine** (>0.95 mol per mol diester) to give the morpholinium salt of ROCOCH2C[:C(CN)2]CH:C(OR)O-, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with BrCH2CO2R' (R' = e.g., Me or Et) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K2CO3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with Sr(OH)2 at reflux in water for ≥ 5 h to give strontium ranelate and its hydrates. Thus, the octahydrate of strontium ranelate was prepared by this method (96% yield and 98% purity in final step).

IT **674773-13-8P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(for industrial preparation of strontium ranelate and its hydrates)

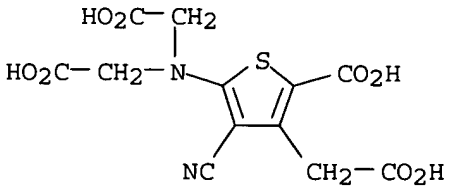
RN 674773-13-8 HCAPLUS

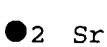
CN 3-Thiopheneacetic acid, 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



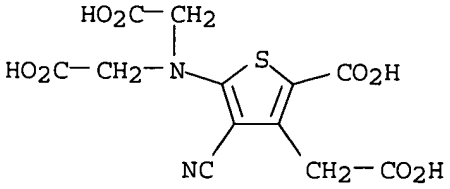
IT **135459-87-9P**, Strontium ranelate **674773-07-0P**
674773-15-0P
RL: IMF (Industrial manufacture); PREP (Preparation)
(industrial preparation of)

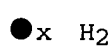
RN 135459-87-9 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (9CI) (CA INDEX NAME)

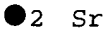




RN 674773-07-0 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2), hydrate (9CI) (CA INDEX NAME)

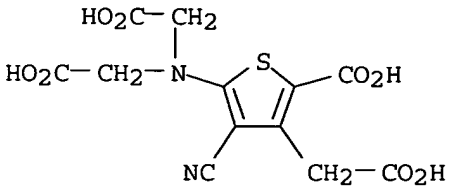






RN 674773-15-0 HCAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-,

strontium salt (1:2), octahydrate (9CI) (CA INDEX NAME)



●8 H_2O

●2 Sr

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s strontium ranelate
        177659 STRONTIUM
             4 STRONTIUMS
        177660 STRONTIUM
                  (STRONTIUM OR STRONTIUMS)
            47 RANELATE
L7          46 STRONTIUM RANELATE
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L10         7 L7 AND PY<=2002

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L8   ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:240650  HCAPLUS
DOCUMENT NUMBER:         142:422811
TITLE:                   Strontium ranelate: A novel mode
                         of action leading to renewed bone quality
```

AUTHOR(S): Ammann, Patrick
CORPORATE SOURCE: Division of Bone Diseases, WHO Collaborating Center for Osteoporosis Prevention, Department of Rehabilitation and Geriatrics, University Hospital of Geneva, Geneva, 1211/14, Switz.
SOURCE: Osteoporosis International (2005), 16(Suppl. 1), S11-S15
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer London Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Various bone resorption inhibitors and bone stimulators have been shown to decrease the risk of osteoporotic fractures. However, there is still a need for agents promoting bone formation by inducing pos. uncoupling between bone formation and bone resorption. In vitro studies have suggested that **strontium ranelate** enhances osteoblast cell replication and activity. Simultaneously, **strontium ranelate** dose-dependently inhibits osteoclast activity. In vivo studies indicate that **strontium ranelate** stimulates bone formation and inhibits bone resorption and prevents bone loss and/or promotes bone gain. This pos. uncoupling between bone formation and bone resorption results in bone gain and improvement in bone geometry and microarchitecture, without affecting the intrinsic bone tissue quality. Thus, all the determinants of bone strength are pos. influenced. In conclusion, **strontium ranelate**, a new treatment of postmenopausal osteoporosis, acts through an innovative mode of action, both stimulating bone formation and inhibiting bone resorption, resulting in the rebalancing of bone turnover in favor of bone formation. **Strontium ranelate** increases bone mass while preserving the bone mineralization **process**, resulting in improvement in bone strength and bone quality.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:253137 HCAPLUS
DOCUMENT NUMBER: 140:287258
TITLE: **Process** for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

WO 2004029035	A1	20040408	WO 2003-FR2776		20030922

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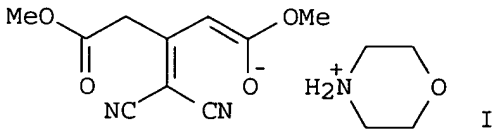
JP 2004269495	A2	20040930	JP 2003-330438	20030922
AT 286041	E	20050115	AT 2003-292317	20030922
ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
SG 110070	A1	20050428	SG 2003-5554	20030924

PRIORITY APPLN. INFO.: FR 2002-11764 A 20020924
OTHER SOURCE(S): CASREACT 140:287258
GI



I

AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of morpholine per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially **strontium ranelate** and its hydrates, is claimed.

L8 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:252227 HCAPLUS
DOCUMENT NUMBER: 140:270729
TITLE: **Process** for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr
SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059134	A1	20040325	US 2003-669302	20030924
FR 2844797	A1	20040326	FR 2002-11765	20020924
FR 2844797	B1	20041022		
EP 1403265	A1	20040331	EP 2003-292318	20030922
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WO 2004029034	A1	20040408	WO 2003-FR2775	20030922
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NZ 528401	A	20040528	NZ 2003-528401	20030923
ZA 2003007411	A	20040707	ZA 2003-7411	20030923
BR 2003004203	A	20040824	BR 2003-4203	20030923
CN 1500784	A	20040602	CN 2003-134812	20030924
SG 110069	A1	20050428	SG 2003-5553	20030924

PRIORITY APPLN. INFO.: FR 2002-11765 A 20020924
OTHER SOURCE(S): CASREACT 140:270729; MARPAT 140:270729
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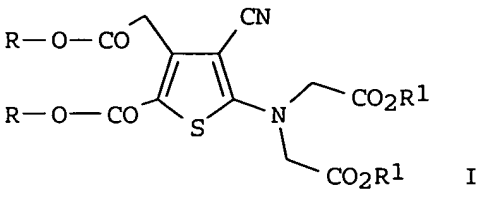

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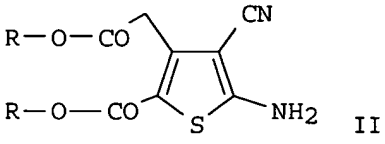


II

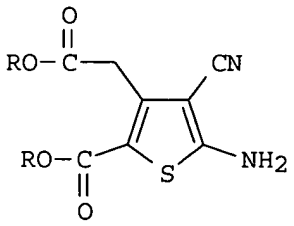
AB Tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid [I; R, R1 = (un)branched C1-6 alkyl] are prepared in high yield and selectivity by the alkylation of the corresponding 5-amino compound (II) with an alkyl bromoacetate ester BrCH2CO2R1 in the presence of a catalytic amount of a quaternary ammonium compound, potassium carbonate acid scavenger at reflux in an organic solvent, the reaction mixture is then concentrated by distillation, an a nonsolvent added to cause precipitation of the product with cooling. The synthesis of bivalent salts of ranelic acid, and especially **strontium ranelate** and its hydrates, is claimed.

L8 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:249307 HCAPLUS
DOCUMENT NUMBER: 140:272696
TITLE: New process for industrial synthesis of **strontium ranelate** and its hydrates
INVENTOR(S): Vaysse, Ludot Lucile; Lecouve, Jean Pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
SOURCE: Fr. Demande, 22 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

WO 2004029036 A1 20040408 WO 2003-FR2777 20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
JP 2004149516 A2 20040527 JP 2003-330440 20030922
CA 2442878 AA 20040324 CA 2003-2442878 20030923
ZA 2003007409 A 20040707 ZA 2003-7409 20030923
NZ 528402 A 20040730 NZ 2003-528402 20030923
BR 2003004213 A 20040831 BR 2003-4213 20030923
US 2004063972 A1 20040401 US 2003-669301 20030924
CN 1496986 A 20040519 CN 2003-134813 20030924
SG 110071 A1 20050428 SG 2003-5555 20030924
PRIORITY APPLN. INFO.: FR 2002-11763 A 20020924
OTHER SOURCE(S): MARPAT 140:272696
GI



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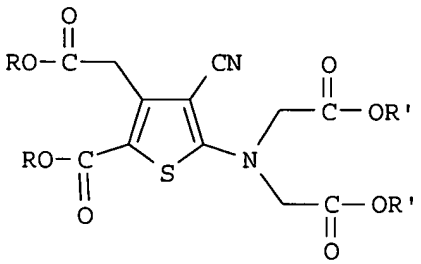

II

AB An industrial **process** for the synthesis of **strontium ranelate** and its hydrates consists of: reaction of RO2CCH2COCH2CO2R (R = linear or branched C1-6 alkyl) with malononitrile (NCCH2CN) in MeOH in presence of morpholine (>0.95 mol per mol diester) to give the morpholinium salt of ROCOCH2C[:C(CN)2]CH:C(OR)O-, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with BrCH2CO2R' (R' = e.g., Me or Et) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K2CO3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with Sr(OH)2 at reflux in water for ≥ 5 h to give **strontium ranelate** and its hydrates. Thus, the octahydrate of **strontium ranelate** was prepared by this method (96% yield and 98% purity in final step).
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:371214 HCAPLUS
DOCUMENT NUMBER: 139:289279
TITLE: Is the calcium receptor a molecular target for the actions of strontium on bone?
AUTHOR(S): Brown, Edward M.
CORPORATE SOURCE: Department of Medicine, Endocrine-Hypertension

Division and Membrane Biology Program, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Osteoporosis International (2003), 14(Suppl. 3), S25-S34
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The extracellular calcium-sensing receptor (CaR) plays key roles in maintaining extracellular calcium homeostasis by enabling several of the cells and tissues involved in this **process** to sense small changes in Ca2+o and to respond with changes in cellular function that will restore Ca2+o to its normal level. The chief cells of the parathyroid gland and the thyroidal C-cells, for example, respond to decreases in Ca2+o with increased secretion of the Ca2+o-elevating hormone, parathyroid hormone (PTH), and decreased secretion of the Ca2+o-lowering hormone, calcitonin, resp. The cells of the renal distal tubule are likewise capable of sensing Ca2+o and respond to decreases in Ca2+o with increased tubular resorption of Ca2+ and vice versa, alterations in tubular function that will contribute to normalization of Ca2+o. The skeleton also plays key roles in maintaining Ca2+o homeostasis and both osteoblasts and osteoclasts can sense Ca2+o, with elevations in Ca2+o promoting bone formation and inhibiting bone resorption. It has been suggested that Sr2+ could act on bone via the CaR; however, the mol. mechanisms through which Ca2+o and Sr2+o exert these actions on bone cells remain controversial. Therefore, identifying their mol. target(s) would have significant implications for the treatment of bone loss. Ideally, therapies should simultaneously inhibit bone resorption while stimulating bone formation. Administration of strontium produces exactly those effects. Previous studies with dispersed bovine parathyroid cells as well as a preliminary study using CaR-transfected CHO cells indicate that Sr2+o is an agonist of the CaR, albeit with slightly lower efficacies and potencies than Ca2+o. Given that Sr2+o is distributed preferentially in bone, therefore, an action of this divalent cation on the CaR in bone cells represents one possible mechanism by which **strontium ranelate**, a new antiosteoporotic drug, exerts it skeletal actions in vivo.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:315356 HCAPLUS
DOCUMENT NUMBER: 135:174574
TITLE: Incorporation and distribution of strontium in bone
AUTHOR(S): Dahl, S. G.; Allain, P.; Marie, P. J.; Mauras, Y.; Boivin, G.; Ammann, P.; Tsouderos, Y.; Delmas, P. D.; Christiansen, C.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Tromso, Tromso, Norway
SOURCE: Bone (New York, NY, United States) (2001), 28(4), 446-453
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 77 refs. The distribution and incorporation of strontium into bone has been examined in rats, monkeys, and humans after oral administration of strontium (either strontium chloride or **strontium ranelate**). After repeated administration for

a sufficient period of time (at least 4 wk in rats), strontium incorporation into bone reaches a plateau level. This plateau appears to be lower in females than in males due to a difference in the absorption **process.** Steady-state plasma strontium levels are reached more rapidly than in bones, and within 10 days in the rat. The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated, and the strontium content of the lumbar vertebra may be estimated from iliac crest bone biopsies in monkeys. The strontium levels in bone also vary according to the bone structure, and higher amts. of strontium are found in cancellous bone than in cortical bone. Furthermore, at the crystal level, higher concns. of strontium are observed in newly formed bone than in old bone. After withdrawal of treatment, the bone strontium content rapidly decreases in monkeys. The relatively high clearance rate of strontium from bone can be explained by the mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium. After treatment withdrawal, strontium exchanged onto the crystal is rapidly eliminated, which leads to a rapid decrease in total bone strontium levels. In summary, incorporation of strontium into bone, mainly by exchange onto the crystal surface, is dependent on the duration of treatment, dose, gender, and skeletal site. Nevertheless, bone strontium content is highly correlated with plasma strontium levels and, in bone, between the different skeletal sites.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:93795 HCAPLUS
DOCUMENT NUMBER: 135:117163
TITLE: **Strontium ranelate** increases cartilage matrix formation
AUTHOR(S): Henrotin, Y.; Labasse, A.; Zheng, S. X.; Galais, Ph.; Tsouderos, Y.; Crielaard, J. M.; Reginster, J. Y.
CORPORATE SOURCE: Bone and Cartilage Metabolism Research Unit, University Hospital, Liege, Belg.
SOURCE: Journal of Bone and Mineral Research (2001), 16(2), 299-308
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on previous studies showing that **strontium ranelate** (S12911) modulates bone loss in osteoporosis, it could be hypothesized that this drug would also be effective on cartilage degradation in osteoarthritis (OA). This was investigated in vitro on normal and OA human chondrocytes, treated or not treated with interleukin-1β (IL-1β). This model mimics, in vitro, the imbalance between chondroformation and chondroresorption **processes** observed in vivo in OA cartilage. Chondrocytes were isolated from cartilage by enzymic digestion and cultured for 24-72 h with 10-4-10-3M **strontium ranelate**, 10-3M calcium ranelate, or 2 + 10-3M SrCl2, with or without IL-1β or insulin-like growth factor I (IGF-I). Stromelysin activity and stromelysin content were assayed by spectrofluorometry and enzyme-amplified sensitivity immunoassay, resp. Proteoglycans (PG) were quantified by RIA. Newly synthesized glycosaminoglycans were quantified by labeled sulfate (Na235SO4) incorporation. This method allowed the PG size after exclusion chromatog.

to be determined **Strontium ranelate**, calcium ranelate, and SrCl2 did not modify stromelysin synthesis even in the presence of IL-1β. Calcium ranelate induced stromelysin activation, whereas the strontium compds. were ineffective. **Strontium ranelate** and SrCl2 both strongly stimulated PG production, suggesting an ionic effect of strontium independent of the organic moiety. Moreover, 10-3M **strontium ranelate** increased the stimulatory effect of IGF-I (10-9M) on PG synthesis but did not reverse the inhibitory effect of IL-1β. Thus, **strontium ranelate** strongly stimulates human cartilage matrix formation in vitro by a direct effect effect of the strontium ion, without stimulating chondroresorption. This finding provides a preclin. basis for in vivo testing of **strontium ranelate** in OA.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:253137 HCAPLUS
DOCUMENT NUMBER: 140:287258
TITLE: Process for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates
INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2003004194	A	20040908	BR 2003-4194	20030922
JP 2004269495	A2	20040930	JP 2003-330438	20030922
AT 286041	E	20050115	AT 2003-292317	20030922

ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
SG 110070	A1	20050428	SG 2003-5554	20030924

PRIORITY APPLN. INFO.: FR 2002-11764 A 20020924
OTHER SOURCE(S): CASREACT 140:287258
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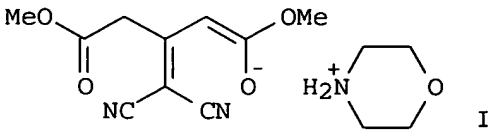


I

AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of **morpholine** per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially **strontium ranelate** and its hydrates, is claimed.

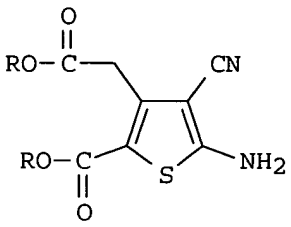
L9 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:249307 HCAPLUS
DOCUMENT NUMBER: 140:272696
TITLE: New process for industrial synthesis of **strontium ranelate** and its hydrates
INVENTOR(S): Vaysse, Ludot Lucile; Lecouve, Jean Pierre; Langlois, Pascal
PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
SOURCE: Fr. Demande, 22 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029036	A1	20040408	WO 2003-FR2777	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,				

PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

JP 2004149516	A2	20040527	JP 2003-330440		20030922
CA 2442878	AA	20040324	CA 2003-2442878		20030923
ZA 2003007409	A	20040707	ZA 2003-7409		20030923
NZ 528402	A	20040730	NZ 2003-528402		20030923
BR 2003004213	A	20040831	BR 2003-4213		20030923
US 2004063972	A1	20040401	US 2003-669301		20030924
CN 1496986	A	20040519	CN 2003-134813		20030924
SG 110071	A1	20050428	SG 2003-5555		20030924
PRIORITY APPLN. INFO.:			FR 2002-11763	A	20020924

OTHER SOURCE(S): MARPAT 140:272696
GI



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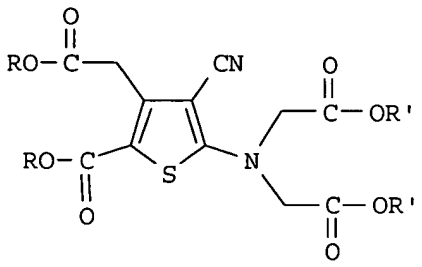

II

AB An industrial process for the synthesis of **strontium ranelate** and its hydrates consists of: reaction of RO2CCH2COCH2CO2R (R = linear or branched C1-6 alkyl) with malononitrile (NCCH2CN) in MeOH in presence of **morpholine** (>0.95 mol per mol diester) to give the morpholinium salt of ROCOCH2C[:C(CN)2]CH:C(OR)O-, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with BrCH2CO2R' (R' = e.g., Me or Et) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K2CO3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with Sr(OH)2 at reflux in water for ≥ 5 h to give **strontium ranelate** and its hydrates. Thus, the octahydrate of **strontium ranelate** was prepared by this method (96% yield and 98% purity in final step).

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l10 ibib abs hitstr tot

L10 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:915149 HCAPLUS
DOCUMENT NUMBER: 138:337014
TITLE: Prevention of Early Postmenopausal Bone Loss by **Strontium Ranelate**: The Randomized, Two-Year, Double-Masked, Dose-Ranging, Placebo-Controlled PREVOS Trial

AUTHOR(S): Reginster, J. Y.; Deroisy, R.; Dougados, M.; Jupsin, I.; Colette, J.; Roux, C.
CORPORATE SOURCE: Bone and Cartilage Unit, University of Liege, Liege, Belg.
SOURCE: Osteoporosis International (**2002**), 13(12), 925-931
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Early postmenopausal women (n = 160) were randomised to receive placebo or **strontium ranelate** (SR) 125 mg/day, 500 mg/day or 1 g/day for 2 yr (40 participants per group). All participants received calcium 500 mg/day. The primary efficacy parameter was the percent variation in lumbar bone mineral d. (BMD), measured using dual-energy X-ray absorptiometry. Secondary efficacy criteria included hip BMD and biochem. markers of bone turnover. At month 24, SR 1 g/day significantly increased lumbar BMD compared with placebo [mean (SD) +5.53% (5.12); p<0.001] for measured values and [mean (SD) +1.41% (5.33%); p<0.05] for values adjusted for bone strontium content. The annual increase for adjusted values was +0.66% compared with -0.5% with placebo, with an overall beneficial effect after 2 yr of about 2.4% with SR 1 g/day relative to placebo. There were no other significant between-group differences in adjusted lumbar BMD. Femoral neck and total hip BMD were also significantly increased at month 24 with SR 1 g/day compared with placebo [mean (SD): +2.46% (4.78) and +3.21% (4.68), resp.; both p<0.001)]. SR 1 g/day significantly increased bone alkaline phosphatase at all time points (p<0.05) compared with baseline and between-group anal. showed a significant increase, compared with placebo, at month 18 (p = 0.048). No effect on markers of bone resorption was observed SR was as well tolerated as placebo. The min. does at which SR is effective in preventing bone loss in early postmenopausal non-osteoporotic women is therefore 1 g/day.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:622852 HCAPLUS
DOCUMENT NUMBER: 138:180010
TITLE: **Strontium ranelate** in osteoporosis
AUTHOR(S): Reginster, J.-Y.
CORPORATE SOURCE: WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases, Liege, Belg.
SOURCE: Current Pharmaceutical Design (**2002**), 8(21), 1907-1916
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:520657 HCAPLUS
DOCUMENT NUMBER: 138:100871
TITLE: Long-term treatment with **strontium ranelate** increases vertebral bone mass without deleterious effect in mice

AUTHOR(S): Delannoy, P.; Bazot, D.; Marie, P. J.
CORPORATE SOURCE: INSERM U349 affiliated CNRS, Lariboisiere Hospital, Paris, 75475, Fr.
SOURCE: Metabolism, Clinical and Experimental (**2002**), 51(7), 906-911
CODEN: METAAJ; ISSN: 0026-0495
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was previously shown that **strontium ranelate** (SR; S12911-PROTO, Institut de Recherches Internationales Servier, Courbevoie, France) can modulate bone metabolism in rats and mice. To determine the long-term effects of SR on vertebral bone metabolism in adult mice, the compound or the vehicle was given in the diet to normal male and female mice for 104 wk at the dose of 200, 600, or 1,800 mg/kg/d corresponding to 0.78, 2.34 or 7.01 mmol Sr2+/kg/d. SR dose-dependently increased plasma strontium concentration, as well as exposure to the drug. Histomorphometric analyses of indexes of bone volume, bone formation, and resorption were determined in the endosteal vertebral bone. SR significantly increased the trabecular bone volume by 25% and 59% in females treated with SR 600 and 1,800 mg/kg/d, resp. This was associated with a 27% and 62% increase in mineralized bone volume Bone volume was also significantly increased by 17% and 38% in male mice treated with SR 200 and 1,800 mg/kg/d, resp. In parallel, SR increased the osteoblastic surface by 131% in males. In addition to this stimulatory effect on bone formation, a 52% decrease in osteoclastic surface, and a dose-dependent decrease in osteoclastic number (30% to 47%), was observed in female mice. Finally, SR even at the highest dose tested did not alter the osteoid thickness, indicating no deleterious effect on bone mineralization. Altogether, these findings show that SR simultaneously increases bone formation and decreases bone resorption in male or female mice, which results in increased vertebral bone mass in both genders without deleterious effect on bone mineralization.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:355260 HCAPLUS
DOCUMENT NUMBER: 137:57516
TITLE: **Strontium ranelate**: Dose-dependent effects in established postmenopausal vertebral osteoporosis-A 2-year randomized placebo controlled trial
AUTHOR(S): Meunier, P. J.; Slosman, D. O.; Delmas, P. D.; Sebert, J. L.; Brandi, M. L.; Albanese, C.; Lorenc, R.; Pors-Nielsen, S.; De Vernejoul, M. C.; Roces, A.; Reginster, J. Y.
CORPORATE SOURCE: Hopital Edouard Herriot, Lyon, 69437, Fr.
SOURCE: Journal of Clinical Endocrinology and Metabolism (**2002**), 87(5), 2060-2066
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the **strontium ranelate** (SR) for treatment of osteoporosis (STRATOS) trial was to investigate the efficacy and safety of different doses of SR, a novel agent in the treatment of postmenopausal osteoporosis. A randomized, multicenter, double-blind, placebo-controlled

trial was undertaken in 353 osteoporotic women with at least one previous vertebral fracture and a lumbar T-score <-2.4. Patients were randomized to receive placebo, 0.5 g, 1 g, or 2 g SR/d for 2 yr. The primary efficacy endpoint was lumbar bone mineral d. (BMD), assessed by dual-energy x-ray absorptiometry. Secondary outcome measures included femoral BMD, incidence of new vertebral deformities, and biochem. markers of bone metabolism Lumbar BMD, adjusted for bone strontium content, increased in a dose-dependent manner in the intention-to-treat population: mean annual slope increased from 1.4% with 0.5 g/d SR to 3.0% with 2 g/d SR, which was significantly higher than placebo ($P < 0.01$). There was a significant reduction in the number of patients experiencing new vertebral deformities in the second year of treatment with 2 g/d SR [relative risk 0.56; 95% confidence interval (0.35; 0.89)]. In the 2 g/d group, there was a significant increase in serum levels of bone alkaline phosphatase, whereas urinary excretion of cross-linked N-telopeptide, a marker of bone resorption, was lower with SR than with placebo. All tested doses were well tolerated; the 2 g/d dose was considered to offer the best combination of efficacy and safety. In conclusion, SR therapy increased vertebral BMD and reduced the incidence of vertebral fractures.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:591786 HCAPLUS
DOCUMENT NUMBER: 136:363762
TITLE: **Strontium ranelate** inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (Macaca fascicularis)
AUTHOR(S): Buehler, J.; Chappuis, P.; Saffar, J. L.; Tsouderos, Y.; Vignery, A.
CORPORATE SOURCE: Departments of Orthopedics and Rehabilitation, and Cell Biology, Yale University School of Medicine, New Haven, CT, USA
SOURCE: Bone (New York, NY, United States) (**2001**), 29(2), 176-179
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Strontium ranelate** (S12911) has previously been shown to stimulate bone formation and inhibit bone resorption in rats. To determine whether **strontium ranelate** affects normal bone remodeling, we studied the effect of **strontium ranelate** on alveolar bone in monkeys. **Strontium ranelate**, at dosages of 100, 275, and 750 mg/kg per day, or vehicle, were given by gavage to 31 normal adult monkeys (Macaca fascicularis) (15 males, 16 females), aged 3-4 yr. Treatment for 6 mo with **strontium ranelate** resulted in an increase in plasma strontium concentration Histomorphometric analyses of indexes of bone formation and resorption were determined in standardized areas of alveolar bone. Treatment with **strontium ranelate** decreased the histomorphometric indexes of bone resorption (osteoclast surface and number) with a maximal significant effect at the highest dose tested. In contrast to this inhibitory effect on bone resorption, **strontium ranelate** maintained bone formation. Although the amount of osteoid tended to increase, **strontium ranelate**, even at the highest dose, had no deleterious effect on bone mineralization, as evaluated by mineral apposition rate and osteoid thickness. These findings show that **strontium ranelate** decreases indexes of bone resorption

while maintaining bone formation in the alveolar bone in monkeys.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:315356 HCAPLUS
DOCUMENT NUMBER: 135:174574
TITLE: Incorporation and distribution of strontium in bone
AUTHOR(S): Dahl, S. G.; Allain, P.; Marie, P. J.; Mauras, Y.; Boivin, G.; Ammann, P.; Tsouderos, Y.; Delmas, P. D.; Christiansen, C.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Tromso, Tromso, Norway
SOURCE: Bone (New York, NY, United States) (**2001**), 28(4), 446-453
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 77 refs. The distribution and incorporation of strontium into bone has been examined in rats, monkeys, and humans after oral administration of strontium (either strontium chloride or **strontium ranelate**). After repeated administration for a sufficient period of time (at least 4 wk in rats), strontium incorporation into bone reaches a plateau level. This plateau appears to be lower in females than in males due to a difference in the absorption process. Steady-state plasma strontium levels are reached more rapidly than in bones, and within 10 days in the rat. The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated, and the strontium content of the lumbar vertebra may be estimated from iliac crest bone biopsies in monkeys. The strontium levels in bone also vary according to the bone structure, and higher amts. of strontium are found in cancellous bone than in cortical bone. Furthermore, at the crystal level, higher concns. of strontium are observed in newly formed bone than in old bone. After withdrawal of treatment, the bone strontium content rapidly decreases in monkeys. The relatively high clearance rate of strontium from bone can be explained by the mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium. After treatment withdrawal, strontium exchanged onto the crystal is rapidly eliminated, which leads to a rapid decrease in total bone strontium levels. In summary, incorporation of strontium into bone, mainly by exchange onto the crystal surface, is dependent on the duration of treatment, dose, gender, and skeletal site. Nevertheless, bone strontium content is highly correlated with plasma strontium levels and, in bone, between the different skeletal sites.
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:93795 HCAPLUS
DOCUMENT NUMBER: 135:117163
TITLE: **Strontium ranelate** increases cartilage matrix formation
AUTHOR(S): Henrotin, Y.; Labasse, A.; Zheng, S. X.; Galais, Ph.; Tsouderos, Y.; Crielaard, J. M.; Reginster, J. Y.
CORPORATE SOURCE: Bone and Cartilage Metabolism Research Unit, University Hospital, Liege, Belg.

SOURCE: Journal of Bone and Mineral Research (2001), 16(2), 299-308
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on previous studies showing that **strontium ranelate** (S12911) modulates bone loss in osteoporosis, it could be hypothesized that this drug would also be effective on cartilage degradation in osteoarthritis (OA). This was investigated in vitro on normal and OA human chondrocytes, treated or not treated with interleukin-1β (IL-1β). This model mimics, in vitro, the imbalance between chondroformation and chondroresorption processes observed in vivo in OA cartilage. Chondrocytes were isolated from cartilage by enzymic digestion and cultured for 24-72 h with 10-4-10-3M **strontium ranelate**, 10-3M calcium ranelate, or 2 + 10-3M SrCl2, with or without IL-1β or insulin-like growth factor I (IGF-I). Stromelysin activity and stromelysin content were assayed by spectrofluorometry and enzyme-amplified sensitivity immunoassay, resp. Proteoglycans (PG) were quantified by RIA. Newly synthesized glycosaminoglycans were quantified by labeled sulfate (Na235SO4) incorporation. This method allowed the PG size after exclusion chromatog. to be determined **Strontium ranelate**, calcium ranelate, and SrCl2 did not modify stromelysin synthesis even in the presence of IL-1β. Calcium ranelate induced stromelysin activation, whereas the strontium compds. were ineffective. **Strontium ranelate** and SrCl2 both strongly stimulated PG production, suggesting an ionic effect of strontium independent of the organic moiety. Moreover, 10-3M **strontium ranelate** increased the stimulatory effect of IGF-I (10-9M) on PG synthesis but did not reverse the inhibitory effect of IL-1β. Thus, **strontium ranelate** strongly stimulates human cartilage matrix formation in vitro by a direct effect effect of the strontium ion, without stimulating chondroresorption. This finding provides a preclin. basis for in vivo testing of **strontium ranelate** in OA.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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